(12) UK Patent Application (19) GB (11) 2 098 506 A

(21) Application No 8127345
(22) Date of filing 10 Sep 1981
(30) Priority data
(31) 263788
(32) 14 May 1981
(33) United States of America (US)
(43) Application published 24 Nov 1982
(51) INT CL³ A61F 1/00
(52) Domestic classification B2E 1733 423T M
(56) Documents cited None
(58) Field of search B2E
(71) Applicant
Biomed Research Inc.,
8733 Beverly Boulevard,
Los Angeles,
California 90048,
United States of America
(72) Inventor
Lester M. Morrison
(74) Agents
J. A. Kemp and Co.,
14 South Square,
Gray's Inn,
London,
WC1R 5EU

(54) **Drug coated materials**

(57) A transplant, implant, inanimate prosthetic or orthopedic device, surgical instrument or the like when coated with an effective amount of "active" chondroitin sulfate A and/or "active chondroitin sulfate C to mitigate rejection or failure of a transplant or implant.

GB 2 098 506 A

SPECIFICATION

Drug coated materials

The use of "active" chondroitin sulfate A and C, and mixtures of these drugs are known for use in the treatment of a variety of cardiovascular diseases and as preventative therapy for these diseases. These drugs including their method of production are described in Morrison U.S. Patents Nos. 3,895,106 and 3,895,106 issued July 15, 1975. An improved method for the production of these drugs is disclosed in U.K. Patent Application No. 8025221.

It has now been discovered that "active" chondroitin sulfate A, "active" chondroitin sulfate C, and mixtures thereof, have a unique and very different therapeutic use. It has been reported in the literature in numerous instances that organ or tissue transplants are subject to rejection by the human host. This problem is also present to a degree in relation to inanimate implants such as tooth implants, hip prosthesis, intraocular implant, heart valve, etc. It is generally believed that the transplant rejection phenomena is associated with the immune system of the body and/or physiologic processes or surgical procedures. The immune system recognizes the transplanted tissue as foreign and produces antibodies which attack the object foreign to the human host. Surgical failure and physiologic failure may be related to mechanical tissue damage, clotting with decreased blood flow, etc. Various approaches have been followed in attempting to diminish or eliminate the rejection or failure problem.

We have found that "active" chondroitin sulfate A, "active" chondroitin sulfate C, or admixtures of the drugs seems to significantly reduce the tendency of the human body to reject transplants and increase the acceptance of implants.

The rejection of implants is due to additional factors including direct mechanical injury to adjacent tissues, devascularization of tissues with resultant poor oxygen supply, tissue unacceptance of the foreign body whether due to direct lack of adherence of adjacent cells, lack of proper electrostatic forces, or poor regeneration of tissues.

The coating of the foreign bodies and/or host treatment with the drugs of this invention reduces rejection and may result in better acceptance of the implant by the surrounding tissues.

It is believed that this development represents a significant advance in this area of therapy.

The coating of surgical instruments will reduce direct tissue damage resulting from contact with these instruments. Likewise, the coating of indwelling catheters or needles will reduce mechanical damage to contiguous endothelial cells within the vascular channel.

It is believed that this development represents a significant advance in this area of therapy.

The present invention provides a transplant, implant, inanimate prosthetic or orthopedic device, surgical instrument or the like when coated with an effective amount of "active" chondroitin sulfate A and/or "active" chondroitin sulfate C to mitigate rejection or failure of a transplant or implant.

The use of an effective amount of "active" chondroitin sulfate A and/or "active"chondroitin sulfate C mitigates rejection or failure of a transplant or implant in the transplantation or implantation into the body of tissue or organs from the same or another human or animal.

The invention provides a new and improved means for combating the problem of rejection, and stimulating and promoting acceptance of both living and inanimate transplants or implants by the human body.

As used herein, the term "transplant" or "transplantation" refers to the grafting of tissue taken from the same or another person. More specifically, it refers to the operation of transplanting or of applying to a part of the body tissues taken from another body or from another part of the same body. This invention covers the full array of such procedures and is particularly used in heart, kidney, lung and skin transplants. The term "implant" or "implantation" means the placement within the body tissues of a foreign, usually inanimate substance. A hip joint mechanical heart valve, surgical staples and intraocular lens are examples. The implanting of pig tissue into humans for heart valve reconstruction is also contemplated by this invention, whether regarded as an implant or a transplant. The "implant" need not be permanent. Thus, the term "implant" herein is broader than in the conventional sense and includes the use of the drugs to coat surgical instruments just prior to their temporary use in the human body. An indwelling catheter or needle can be beneficially coated with the drugs prior to placement into the patient. Likewise, IV tubing, sutures and even surgical instruments. The coating of implants such as titanium rods to act as a bone, and mechanical metal knee and hip joints is of considerable value. As used herein, a "prosthetic" device refers to any artificial substitute for a missing part, as denture, hand, leg or eye.

While not bound by any theory, it is believed that the present invention improves the implantation in inanimate devices by virtue of the fact that the drug has a negative electrical charge and the implants bear a positive surface charge. The hypothesis is that the drugs lead to the neutralization of the positive charge or create a resultant negative charge which provides for less damage to contiguous cells or tissues. Another likely factor is the lubricating properties of the drugs which seem to increase compatability of the implant with the surrounding living tissues and prevents direct mechanical cell damage. The lubricating properties of the drugs via direct application to intraperitoneal surfaces or structures at the time of abdominal surgical procedures may reduce the occurrence of post-operative adhesions.

These and other objects and advantages of this invention will be apparent from the more detailed description which follows.

Description of the preferred embodiments

The present invention is applicable to the transplantation, human-to-human, animal-to-human, of all organs and tissues including kidney, heart, lungs, skin, etc. It also appears to be useful in cases of re-attachment of tissues or organs such as in cases requiring the re-attachment of the cornea or retina.

The drug can be administered beginning three to four days prior to the transplantation or implant and can usefully be continued for weeks, months, or even years thereafter. In any case, the drug would be administered essentially concurrently with transplantation. The mode of administration is by injectible aqueous solution, orally, or the like. The administration in the case of major organ transplant is intra-peritoneally, intravenously or orally or powder, ointment, eye drops, as an aqueous solution. The dosage would be an effective amount on the order of 0.1 to 10 or more grams per 24 hour period.

It is also beneficial to soak, infuse, coat or incubate the transplant or implant, that is, the skin, heart, kidney or lung or artificial, synthetic devices with the drug just before transplantation or implant in the human recipient.

In the case of inanimate implants for the eye or joints such as intraocular lens, tooth implant, knee implant, orthopedic plates or pins, hip prosthesis, the inanimate transplant or implant, can be beneficially coated with the drug just prior to placement in the human body, and fortified periodically by local applications or injections and the like of the "active" drug.

The soaking or coating procedures just described are usually in addition to the more protracted systemic administration of the drug earlier described hereinabove. The solution used to coat is a 1 to 30% by weight of a physiologically compatible, normally aqueous, solution of the drug. The drug can be applied to the eye in drop form. The drugs can also be combined with conventional carriers to form a viscous ointment and coated onto a skin transplant to mitigate rejection. The drugs used in the practice of this invention are prepared as follows:

Example 1

On hundred pounds of trimmed bovine trachea was chopped into 1 inch square segments and added to about 50 gallons of deionized water in a tank. The pH was adjusted to about 4.5 by addition of approximately 400 ml of glacial acetic acid. The resulting suspension was agitated while the contents of the tank was raised to about 50°C. One and one-quarter pounds of pepsin was added and the agitation continued for 30 minutes. Another 50 gallons of de-ionized water was added to the tank and mild stirring continued for 12 hours at 50°C until the tracheal cartilage is freed of connective tissue. The temperature of the suspension is then raised to 80°C and a fat layer formed on the top of the liquid. The digestion liquor was drained off through basket centrifuge and discarded.

The remaining solids were twice washed with 50 gallons of hot water (60-80°C). A sodium hydroxide solution was prepared by adding 1.5 lbs. of NaOH to 5 gallons of de-ionized water in a tank. The twice washed solids were added to the sodium hydroxide solution, and the volume adjusted with de-ionized water to 12 gallons and the pH to 9—10. The contents of the tank was agitated for 12 hours at 37°C. The pH was then adjusted to 6.5 with glacial acetic acid. The liquid was heated to boiling and then permitted to cool. The liquid was filtered through a basket centrifuge and the filtrate collected and retained. To the retained filtrate was added 1.5 pounds of cetyl pyridinium chloride followed by stirring for 30 minutes. The liquid was allowed to stand for 16 hours. A precipitate from the supernatant was decanted and the precipitate collected by continuous centrifugation in a Sharples centrifuge. The collected precipitate was in 5 gallons of 0.5N sodium hydroxide. Ten gallons of methanol was added and allowed to stand for 12 hours at room temperature. The precipitate formed was again collected by continuous centrifugation and washed with 5 gallons of methanol. The precipitate was dissolved in two gallons distilled water, the pH adjusted to 7.0 with glacial acetic acid and 1/4 pound of sodium chloride was added, followed by stirring. Four gallons of methanol was added and agitation was carried out for 15 minutes. After standing for 12 hours at room temperature, a precipitate had formed which was collected by centrifugation. The precipitate was dried under vacuum. Analysis showed the precipitate to be essentially CSA. The material manifested a prolongation of plasma thrombus formation time 6 to 12 hours after administration in rabbits as described by the Chandler loop method of over 80%.

A sterile solution suitable for intravenous injection or local applicable is obtained by dissolving 125 mg. of the drug in 2.5 ml of USP sterile water for injection. If necessary, the solution can be finally sterilized by passing it through a sterilizing membrane filter. When donor human skin was soaked for five minutes in this solution and applied to an area of third degree burn, the rejection was reduced.

An ointment containing the drugs is prepared by adding from about 1 to 30% by weight of the drug to a vehicle or carrier which is normally viscous such as petroleum jelly or made viscous by the addition of emulsifiers or thickeners to water. The vehicle or carrier are usually composed of various mixtures of fats, waxes, animal and vegetable oils, and solid or liquid hydrocarbons.

Example 2

One starting material for the preparation of active chondroitin sulfate A is bovine trachea. This

material is obtained from the slaughter houses as soon as possible after the animals are slaughtered. It is then frozen until processed. In processing, it is trimmed free of tissue and finely ground. This ground tissue is defatted with five parts of acetone. Two extractions are made to reduce the fat content to approximately 1 percent or less. The defatted material is dried and re-ground. A 5 percent solution of the latter is made up in a 0.1M calcium acetate buffer containing 1 percent papain plus 0.005M cystein hydrochloride and 0.005M disodium versenate as enzyme activators. The entire mixture is maintained at 62°C±3°C for 24 to 30 hours with gentle stirring. Approximately 85 to 95 percent solubilization of the trachea is obtained. This supernatant is decanted and is precipitated with two volumes of acetone. The acetone supernatant is decanted. The remaining precipitated material is dissolved in isotonic saline to make a solution of 3—5 percent. To the latter is added a saturated solution of potassium permanganate in 2 to 5 ml. portions with constant stirring, adding each portion until the purple color has been totally discharged. Depending on the various raw materials started with, this may take anywhere from 50 to 200 ml. of potassium permanganate solution per 6 lbs. of starting raw material. When at the interval between addition and discharge, the color becomes long (sic) (more than 5 minutes), no further permanganate is added. The solution is then allowed to stand overnight to permit flocculation of the manganese dioxide and completion of any reactions. The manganese dioxide is removed either by centrifugation or filtration through a coarse filter paper. The manganese dioxide cake is washed with additional isotonic saline. In some cases the addition of a small amount of formaldehyde or methanol will cause flocculation of manganese dioxide which is then precipitated with one volume of acetone. The resultant oily precipitate is collected by decantation, the solvent evaporated or the cake dissolved in a minimum amount of water and the final product obtained by lyophilization. It appears on paper chromatography to be essentially pure chondroitin sulfate A. Analysis of the product shows a typical chondroitin sulfate A infra-red spectrophotometric absorption curve. Optical rotation determination gives values of $(a)_D^{24}=-24°$; nitrogen content, 3.3%.

Example 3

One starting material for the preparation of active chondroitin sulfate C is shark cartilage. This material obtained in dry form is ground and defatted with three to five parts acetone. One extraction is usually sufficient. This extracted shark cartilage is then treated as indicated above for the dried bovine trachea after the defatting stage.

The drugs prepared as in Example 2 and 3 are useful in all of the procedures described hereinabove.

Having fully described the invention, it is intended that it be limited only by the lawful scope of the appended claims.

Claims

1. A transplant, implant, inanimate prosthetic or orthopedic device, surgical instrument or the like when coated with an effective amount of "active" chondroitin sulfate A and/or "active" chondroitin sulfate C to mitigate rejection or failure of a transplant or implant.

2. A transplant, implant, device, instrument or the like according to claim 1 which has been coated with sterile IV solution of the drug.

3. A transplant, implant, device, instrument or the like according to claim 1 which has been coated with an ointment of the drug.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1982. Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.